UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/762,106 | 02/02/2001 | Dearg S Brown | PM-276502/Z- | 8384 |

9629 7590 12/29/2003

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

| EXAMINER | |
|---|---|
| MCKENZIE, THOMAS C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | 21 |

DATE MAILED: 12/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/762,106 | BROWN ET AL. | |
| | Examiner | Art Unit | |
| | Thomas McKenzie Ph.D. | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *1-3,5,6,8-10 and 12-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9,10 and 12-19* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This action is in response to amendments filed on 10/27/03. Applicant has amended claims 1, 9, 10, 12, and 13. Claims 14-19 are new. Applicants new second claim 17 and claim 18 have been renumbered 18 and 19 respectively as per Rule 126. There are sixteen claims pending and sixteen under consideration. Claims 1-3, 5, 6, 9, 10, 12, and 13 were previously rejected. Objection was made to claim 8. Claims 1-3, 5, 6, and 8 are compound claims. Claim 10 is a composition claim. Claims 12-19 are use claims. Claim 9 is a synthesis claim. This is the fourth action on the merits. The application concerns some amidobenzamide compounds, compositions, and uses thereof. There are two issues, "*in-vivo* cleavable ester" and disease treatment enablement. These will be discussed separately. Applicants remarks concerning changes in policy at the USPTO and the allowance of similar claims in noted. However, the individual facts in this case are germane, not what may be happening in the office.

### *Claim Rejections - 35 USC § 112*

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-3, 5, 6, 9, 10, 12, and 13 remain rejected and claims 14-19 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "*in-*

*vivo* cleavable ester thereof formed on an available carboxy or hydroxy group" in claims 1, 6, 10, 12, and 14-18 indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "*in-vivo* cleavable ester" are molecules whose structure lie outside the subject matter of Formula I, but upon metabolism in the body are converted to active compounds falling within the structural scope of Formula I. The phrase describes the function intended but provides no specific structural guidance to what constitutes an "*in-vivo* cleavable ester". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. Lines 4-13, page 23 list suitable esters, but use open language "for example". The Examiner suggests adding these specific examples to the claim to clarify what Applicants intend.

3. Claims 1-3, 5, 6, 9, 10, 12, and 13 remain rejected and claims 14-19 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the *in vivo* cleavable esters listed in lines 4-13, page 23, does not reasonably provide enablement for making all *in vivo* cleavable esters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention

commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Synthesis of any particular *in vivo* cleavable ester would require identification of which esters are *in vivo* cleavable and devising a new synthesis of each ester. Considering the difficulty of the first step this is a large degree of experimentation. b) The direction concerning the *in vivo* cleavable esters was discussed above. There is no direction as to how to prepare these compounds. c) There is no working example of the identification of any *in vivo* cleavable esters let alone the synthesis of it. d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art with *in vivo* cleavable esters is that it is unknown which esters of which substrate fit the claim limitation. An acetoxymethyl ester of one substrate, which is in vivo cleavable, would not necessarily be so cleavable when applied to a different substrate. f) The artisan using Applicants invention to prepare the claimed compounds would be a process

chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the millions of compounds of claim 1 as well as the presently unknown list of esters embraced by the phrase "*in vivo* cleavable". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Applicants have added the limitation "on an available carboxy or hydroxy group". Applicants also argue that requiring an exhaustive listing of every ester is unreasonable and that only ordinary skill and experimentation are required for the average organic chemist to make an ester from any given alcohol and acid. This is not persuasive. An ester is the reaction product of an alcohol and an acid. The only way to make an ester of the claimed compounds is by reaction with the

appropriate partner "on an available carboxy or hydroxy group". Thus, the added limitation does not change the claim. The gist of these two rejections is what alcohol or acid partner are to be used and how do we know if the resulting ester is *in vivo* cleavable? Applicants have pointed to no reference in the chemical literature showing that it is art-recognized which esters meet these limitations. Without listing the claimed esters, the organic chemist will not understand the meets and bounds of the claimed compound subject matter. The indefiniteness remains despite what was allowed in another case. The U.S. Court of Customs and Patent Appeals wrote *In re Giolito* 188 USPQ 645: "We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been allowed to others. See *In re Margaroli,* 50 CCPA 1400, 318 F.2d 348, 138 USPQ 158 (1963); *In re Wright*, 45 CCPA 1005, 256 F.2d 583, 118 USPQ 287 (1958); *In re Launder*, 41 CCPA 887, 212 F.2d 603, 101 USPQ 391 (1954)".

Similarly, the skilled synthetic chemist does not know what ester he is to make. The skilled organic chemist does not know how much hydrolysis is required for the ester to be considered *in vivo* cleavable. The skilled organic chemist does not know which or how many different living organisms must be

tested to see if any ester is "*in vivo* cleavable". This surely makes the experimentation both extensive and undue.

4. Claim 12 remains rejected under and claims 14 and 15 newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim provide for the use of the compounds of formula I, but the claims do not set forth any steps involved in determining what is "a disease or medical condition mediated by TNF" or which animals require inhibition of TNF. It is unclear what diseases and treatments applicant is intending to encompass. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Lines 15-17, page 1 and 17-23, page 2 list some diseases Applicants regard as TNF related. The lists use open language, so what else is covered by the claim? Black (Ann. Reports Med. Chem.) considers cachexia, sepsis, Crohn's, encephalomyelitis, endotoxemia, and bone resorption as such diseases. Applicants do not list them. Are they covered by the claim or not? Black (Ann. Reports Med. Chem.) hints that all autoimmune diseases are so related. Should an enablement rejection be made over

autoimmune diseases even though Applicants does not list them in his specification?

5. Claim 13 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim provide for the use of the compounds of formula I, but the claims do not set forth any steps involved in determining what is "a disease or medical condition mediated by IL-1, IL-6 or IL-8". It is unclear what diseases and treatments applicant is intending to encompass. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Applicants in lines 8-11, page 50 state their intention to inhibit such cytokines without stating which diseases are to be treated. Lines 15-17, page 1 and 17-23, page 2 discuss IL-1 but are silent as to IL-6 and IL-8. Fogarasi (Orv Hetil.) considers hepatic diseases, non-specific inflammatory bowel diseases (Crohn's disease and ulcerative colitis) and certain autoimmune diseases to be IL-6 related. Yet, Barton (Clin Immunol Immunopathol.) considers acute inflammation, such as toxic or septic shock, cachexia, multiple myeloma, and osteoporosis to be IL-6 related. These are totally

different sets of diseases. Thus, there is confusion in the scientific literature as to which diseases fall into Applicants' claim limitation. None of the diseases listed above are listed in the specification by Applicants as IL-6 related.

6. Claims 12 and 13 remain rejected and claims 14, 15, and 16 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating rheumatoid arthritis and psoriasis, does not reasonably provide enablement for treating all TNF, Il-1, IL-6, or IL-8 mediated diseases. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above. a) Determining if any particular claimed compound would treat any particular TNF, Il-1, IL-6, or IL-8 mediated diseases disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different TNF, Il-1, IL-6, or IL-8 mediated diseases described above, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation.

b) The direction concerning treating TNF, Il-1, IL-6, or IL-8 mediated diseases is found in the lines 15-17, page 1 and 17-23, page 2, which merely states Applicants' intention to do so. Applicants describe formulations in lines 3-18, page

48. Doses required to practice their invention are described in the passage spanning line 19, page 48 to line 6, page 49. A 1,000-fold range of doses is recommended. Since no p38 inhibitor has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are three *in vitro*, one *ex vivo*, and one *in vivo* assay described in the passage spanning line 27, page 42 to line 7, page 47. There is data in only two of the *in vitro* assays for five compounds. It is unclear if these assay are correlated to TNF, Il-1, IL-6, or IL-8 mediated diseases. The *in vivo* assay appears to be prophetic. c) There is no working example of treatment of any disease in man or animals. There are no working examples of formulations. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in p38 enzyme inhibitors, which is the postulated mechanism of action of Applicants compounds, is provided by English (Trends) in figure 1, page 42 who summarizes in which diseases clinical trials have started. Barton (Clin Immunol Immunopathol.) discusses "the possibility of IL-6 both as a therapeutic agent and as a target for antagonists". Clarifying that such use is not presently art-recognized. Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims.

Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the millions of compounds of claim 1 as well as the hundred of diseases embraced by the term TNF, p38, IL-1, IL-6, or IL-8 mediated. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

7. Claims 17 and 18 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating rheumatoid arthritis

and psoriasis, does not reasonably provide enablement for treating all inflammatory diseases. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above, as have Applicants teachings in the specification.

Firstly, for a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

The scope of the claims involves all of the millions of compounds of claim 1. Additionally, the scope of the claim limiataions "anti-inflammatory effect" and "inflammatory disease" is extrodionaryly broad. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the

stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages that have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital

cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Pseudogout, sometimes referred to as calcium pyrophosphate disease (CPPD), is inflammation caused by calcium pyrophosphate (CPP) crystals. It is treated with nonsteroidal anti-inflammatory drugs, corticosteroids, and colchicine.

Sinusitis is the inflammation of the mucosal lining of one or more sinuses. It commonly accompanies upper respiratory viral infections and in most cases requires no treatment.

Pharyngitis (tonsillitis) is an inflammatory illness of the mucous membranes and underlying structures of the throat (nasopharynx, uvula, and soft palate). The illness can be caused by bacteria, viruses, mycoplasmas, fungi, and parasites, and uncertain causes, especially Streptococcus pyogenes, adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, and Mycoplasma pneumoniae. Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). Fungi or viruses can cause the disease. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza. Conjunctivitis (pink eye) is inflammation of the conjunctiva and can be caused by many microorganisms, including staphylococci, Haemophilus influenzae, streptococci, gonococci, and viruses such as adenoviruses. Treatment in all of these cases, when possible, is thus to the underlying infectious agent.

Rheumatoid arthritis is an inflammatory bone disease causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-18 and IL-18, and IFN- .

Pneumonia is an inflammation of the lungs that can be caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), bacteria, fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents.

Other inflammations in the respiratory system include CF, adult respiratory distress syndrome, asthma, and bronchitis.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris,

syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is an inflammation of the outer covering of the brain and spinal cord. Virtually any known infectious agent can cause it. Thus, if it were caused by Haemophilus influenzae or Neisseria meningitis, the antibiotic derivative rifampin would be used.

Encephalitis is an inflammation of the brain itself. It is most often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also takes the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids are an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything that obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia, and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the exterior of the body. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when Neisseria gonorrhoeae is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially Candida albicans), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta-blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder, which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy, and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to Lactobacillus capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis, and cat-scratch disease. Treatment is thus to the underlying cause. For example, diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach

lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee string), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrown hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. The inflammation of acne is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus Propionibacterium acnes, which populate the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), that are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is

known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those, which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms, and treatment (or lack thereof) for inflammation.

Thus, the scope of claims is very broad. It also establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Applicants made no comments concerning the various factors in the enablement rejection. The U.S. Court of Customs and Patent Appeals wrote *In re Wertheim, et al.*, 191 USPQ 90, "we have often repeated, as recently as In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976), it is immaterial in ex parte prosecution whether the same or similar claims have been allowed to others".

Applicants have cited no medical literature stating that it is art-recognized which diseases are covered by their functional limitations. To the contrary, the Examiner has cited art showing disagreement in the medical literature as to what diseases are covered by these terms. There is not even any experimental method of determining the claim boundaries that is guaranteed to produce a definitive answer. Thus, the average physician would not understand the metes and bounds of the claims.

***Allowable Subject Matter***

8. Claim 8 is objected to as being dependent upon a rejected base claim.

***Conclusion***

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date

of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund J. Shah

**Mukund Shah**
**Supervisory Patent Examiner**
**Art Unit 1624**

TCMcK